REMARKS

Upon entry of the foregoing amendments, Claims 15, 16, 19-26, and 49-52 will be pending. Applicants have cancelled Claims 1-14 without prejudice to, or disclaimer of, the subject matter contained therein. Applicants maintain that the cancellation of a claim makes no admission as to its patentability, and reserve the right to pursue the subject matter of the cancelled claims in this or any other patent application. Applicants have amended Claims 15-16, 19, 21, and 49-51 and have added new Claim 52. The amendments add no new matter and are fully supported by the specification as filed. Support for the amendments can be found, for example, on page 19, lines 1-20, page 9, lines 3-5; page 9, lines 30-31, page 11, lines 2-3, page 15, lines 19-21, and elsewhere throughout the specification as originally filed.

The Examiner rejected Claims 1-5, 7, 9, 13, 15-19, 21, 23 and 49 in the Office Action mailed December 26, 2008. Applicants respond below to the specific rejections set forth in the Office Action. For the reasons below, Applicants respectfully traverse.

Response to Election

The Examiner has maintained that the Restriction Requirement mailed March 12, 2008 is proper and final. The Examiner has maintained that Applicants' arguments that the restriction improperly limits the claims to small molecules that either (1) regulate PKCζ transcription or (2) PKCζ translation, and provides Applicants with no outlet for pursuing claims that recite modulation agents that affect functional modulation of the PKCζ expression product are unpersuasive.

During the telephonic interview of February 20, 2008, Examiner Swope agreed that Applicants would be entitled to have small molecule antagonists of PKCζ examined. (See, Supplemental Amendment filed February 25, 2008, page 6). The Restriction Requirement mailed March 12, 2008 does not reflect the agreement reached between Examiner Swope and Applicants' representative on February 20, 2008. As agreed during the telephonic interview of February 20, 2008, the Examiner included (iv) "A small molecule antagonist" as one of the groups of non-protein molecules set forth in (D) of the Restriction. However, the Restriction Requirement mailed March 12, 2008 required Applicants to either (M) regulation of transcription; or (N) regulation of translation. (Office Action mailed March 12, 2008, p 4). As

such, as discussed during the telephonic interview of February 20, 2008, the Restriction improperly omits small molecule antagonists that do not affect the transcription or translation of PKCζ, and instead modulate the activity of the PKCζ expression product.

Applicants note that the impropriety of the restriction is evidenced by the list of modulators from which Applicants were required to choose, as set forth in (D) of the Restriction. Specifically, (D) includes, in addition to (iv) "A small molecule antagonist," (ii) Chelerythrine chloride and (iii) Bisindoylmaleimde, which are specific small molecule antagonists. Accordingly, the Restriction does not make sense, since (iv) small molecule antagonists is generic t, and encompasses (ii) and (iii).

In view of the foregoing, Applicants respectfully request withdrawal of the finality of the Restriction Requirement and issuance of a new Restriction, if necessary, that reflects the agreement reached during the telephonic interview of February 20, 2008.

Rejection Under 35 U.S.C. § 112, second paragraph

The Examiner has rejected Claims 2, 7, 16 and 21 as allegedly being indefinite. Specifically, the Examiner states that the term "said endothelial cell" present in Claims 2 and 16 lack antecedent basis. Further, the Examiner states that the term "and/or" in claims 7 and 21 renders the claims ambiguous.

Applicants' cancellation of Claims 2 and 7 renders the rejection of these claims moot.

Applicants have amended claim 16 to replace the term "said endothelial cell" with the term "said intercellular endothelial cell permeability."

Applicants have replaced the term "and/or" in Claim and 21 with the term "or." Applicants maintain that Claim 21 is not limited to modulation that affects transcription or translation exclusively, but rather note that the claims encompasses modulation that affects both transcription and translation of PKCζ, in addition to modulation that affects transcription but not translation, or translation but not transcription.

Applicants maintain the amendments address and overcome the rejection under 35 U.S.C. § 112, second paragraph, and respectfully request reconsideration and withdrawal of the rejection accordingly.

Rejection Under 35 U.S.C. § 112, first paragraph – written description

The Examiner has rejected Claims 1-5, 7, 9, 13, 15-19, 21, 23 and 49 as allegedly containing subject matter that was not adequately described in the specification under 35 U.S.C. § 112, first paragraph. Specifically, the Examiner states that Applicants' specification does not describe a representative number of non-proteinaceous PKCζ modulating agents in order to provide adequate written description for the genus. According to the Examiner, Applicants disclose "merely one example of a non-proteinaceous PKCζ modulating agent, an inhibitor of thrombin-stimulated permeability of endothelial cells, i.e., angiopoietin-1." (Office Action at 8). The Examiner argues "[h]owever, the specification is silent about how angiopoietin-1 regulates the transcription of PKCζ expression product, let alone modulation by any non-proteinaceous modulating agent other than angiopoietin-1." (*Id.*)(Emphasis added). Accordingly, the Examiner states that 1-5, 7, 9, 13, 15-19, 21, 23 and 49 are not adequately described.

As an initial matter, Applicants note that angiopoietin-1 is not a "non-proteinaceous PKCζ modulating agent," as asserted by the Examiner, but is a protein. Further, as noted by the Examiner, Applicants have demonstrated that angiopoietin-1 inhibition of PKCζ "occur[s] through inhibition of PKCζ translocation and activation." (Office Action at 8, citing Specification, paragraph [0143]; example 4). Thus, the Examiner has acknowledged that angiopoietin-1 is an example of a modulator that modulates that activity of the PKCζ expression product, rather than PKCζ transcription or PKCζ translation. The Examiner's statements regarding the alleged lack of disclosure regarding how angiopoeitin-1 "regulates the transcription of PKCζ expression product" (Office Action at 8), highlights the problem with the Restriction set forth above, in that "modulation of the functional activity of protein kinase Cζ," as recited in the claims, is not limited merely to modulation of transcription or translation of PKCζ, but includes modulation agents that function by regulating the localization, phosphorylation, and the like, that affect the "functional activity of protein kinase Cζ."

Regarding the Examiner's statement that Applicants have only disclosed a single modulation agent of PKCζ, and have therefore failed to disclose a representative number of the genus of non-proteinaceous PKCζ modulation agents, Applicants respectfully note that the Examiner has pointed out several PKCζ modulation agents that were described in Applicants' specification. Specifically, the Examiner states that "the as filed application discloses exemplary

inhibitors of thrombin-stimulated permeability of endothelial cells," including chelerythrine chloride and bisindolylmalemide I." (Office Action at 11). In addition to identifying chelerythrine chloride and bisindolylmalemide I as PKCζ modulation agents, the specification states that calphostin C is a modulator of protein kinase Cζ, (Specification, at paragraph [0140]). Applicants further note that, contrary to the Examiner's assertions, the specification additionally identifies antisense nucleic acids and other nucleic acids as non-proteinaceous modulation agents of protein kinase Cζ. Accordingly, Applicants describe several species of non-proteinaceous modulators of PKCζ functional activity.

In view of the foregoing, Applicants respectfully submit that the specification provides a representative number of non proteinaceous protein kinase Cζ modulation agents to satisfy the written description requirement. Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph accordingly.

Rejection Under 35 U.S.C. § 112, first paragraph – enablement

The Examiner has rejected Claims 1-5, 7, 9, 13, 15-19, 21, 23 and 49 under 35 U.S.C. § 112, second paragraph, as allegedly not being enabled by the specification. Specifically, the Examiner argues that while the specification is enabled for "an *in vitro* method for selectively retarding or preventing thrombin-induced vascular endothelial cell permeability," the specification does not reasonably provide enablement for claims directed to an *in vivo* method of modulating endothelial cell activity. Further, the Examiner notes that the claims encompass modulating agents that function as "positive or negative regulators of transcriptional regulation of the PKCζ gene," (Office Action, at 11), and again argues that the specification only describes "validation of merely one inhibitor of thrombin-stimulated permeability of endothelial cells, *i.e.* angiopoietin-1." The Examiner notes that the specification discloses exemplary inhibitors of thrombin-stimulated permeability of endothelial cells such as chelerythrine chloride and bisindolylmaleimide I, and angiopoietin-1. (*Id.*). The Examiner also states several "widely divergent factors" were known to increase vascular endothelial cell permeability, and notes that the art discloses conflicting results of the role of PKC activation on endothelial cell permeability. As such the Examiner states that the skilled artisan would have to "extensively test many non-proteinaceous modulating agents" to discover which particular agent affected PKCζ.

The Examiner uses the following interpretation of the claims in formulating the rejection under 35 U.S.C. § 112, first paragraph: "claims are broadly interpreted as methods for treating and or preventing any disease characterized by inappropriate endothelial cell activity. . .by administration to a subject an effective amount of an agent to induce a functional [*sic*] ineffective level of PKC." (Office Action at 11). The Examiner has cited several references that allegedly demonstrate the unpredictability of the etiology of diseases and conditions associated with aberrant regulation of endothelial cell activity. (Office Action at pp. 14-15). The Examiner argues that the specification "does not reasonably provide enablement for claims directed to methods of modulating endothelial cell activity with the contemplated use of treating or preventing conditions characterized by inappropriate endothelial cell activity in a subject." (Office Action at 10).

Applicants respectfully submit that the Examiner has improperly imported limitations into the claims, which are not present. Specifically, Applicants note that the present claims do not require therapeutic effects, as suggested by the Examiner. Rather, the claims recite methods of modulating endothelial cell intercellular permeability by contacting the endothelial cell with a proteinaceous or non-proteinaceous modulation agent that modulates the functional activity of protein kinase Cζ in a cell. While Applicants agree that such inhibition could be in the setting of a therapeutic benefit, it is not required by the claims. Applicants need only provide an enabling disclosure for the claimed invention. Therefore, the specification, in addition to other evidence provided by the Applicant, need only demonstrate that one of ordinary skill in the art could perform the claimed method without undue experimentation, *i.e.*, a method of modulation of endothelial cell permeability by contacting the cell with a modulation agent that modulates PKCζ functional activity in the endothelial cell. As set forth below, the skilled artisan would not have to undertake undue experimentation to practice the presently claimed invention.

Applicants' description, including the working examples, provide sufficient guidance regarding how to determine whether and how to modulate endothelial intercellular permeability by modulating the functional activity of protein kinase Cζ, by contacting the endothelial cell with a proteinaceous or non-proteinaceous modulation agent. Specifically, endothelial permeability assays are described in paragraphs [0135], and [140]-[145] provide detailed protocols that can be used to determine whether a modulation agent functions to modulate PKCζ functional activity

and endothelial cell permeability. The assays provided in the specification are widely accepted experimental models for investigating vascular and lymphatic endothelial cell permeability, and, absent specific evidence by the Examiner to the contrary, must be accepted as correlating to *in vivo* embodiments. (See, M.P.E.P. §2164.02, stating that "if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate."). Accordingly, given the guidance provided in the specification, the skilled artisan would have to undertake, at most, routine experimentation, in order to practice the claimed invention.

In view of the foregoing, Applicants respectfully submit that the presently claimed invention is fully enabled by the teachings of the specification. Applicants request reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph accordingly.

Rejection Under 35 U.S.C. § 102(b)

The Examiner has rejected Claims 1-4, 7, 9, 15-18, 21, 23 and 49 as allegedly being anticipated by Hempel et al. (1999) *Circulation* pp. 2523-2529, inasmuch as the claims read on an *in vitro* method for modulating endothelial cell activity through modulating the functional activity of PKCζ. The Examiner argues that Hempel et al. disclose a method of preventing ischemia-induced translocation of PKCα and PKCζ or inhibiting expression of PKC isoforms by nifedipine. The Examiner states that Hempel et al. also disclose inhibition of PKC isoforms with antisense oligodeoxynucleotides, which prevent the transcription of the PKCζ gene product.

As amended, the claims require the modulation of endothelial cell intercellular permeability by contacting the endothelial cell with a proteinaceous or non proteinaceous modulation agent that associates with a protein kinase Cζ expression product or a protein kinase Cζ nucleic acid molecule. Hempel et al. do not disclose the modulation of endothelial cell permeability by contacting an endothelial cell with a proteinaceous or non proteinaceous modulation agent that associates with a protein kinase Cζ expression product or a protein kinase Cζ nucleic acid molecule. Hempel et al. performed experiments with antisense oligonucleotides (ODN) for the PCK isoforms "to analyze which PKC is responsible for the increase in the observed increased endothelial cell permeability upon exposure to ischemia induced by

KCN/DG." (Hempel et al., p. 2526, Col. 2). Hempel et al. showed that treating endothelial cells with anti-PKCα ODN almost completely inhibited ischemia induced endothelial cell permeability. The authors report that blocking expression of any of the other isoforms of PCK had no effect on endothelial cell permeability, noting: "in contrast to the effects of antisense against PCK-α, **antisense ODN against PKC-ε and –ζ did not reduce ischemia-induced permeability significantly.**" (Hempel et al., p. 2526, Col. 2, Fig. 5). Accordingly, the teachings of Hempel et al. do not meet each and every limitation Applicants' presently claimed invention. Because Hempel et al. do not teach a method of modulating endothelial cell intercellular permeability by contacting an endothelial cell with a modulation agent that associates with a protein kinase Cζ expression product or a protein kinase Cζ nucleic acid molecule, as required by Applicants' claims, Hempel et al. does not anticipate the claims.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b).

Rejection Under 35 U.S.C. § 103(a)

The Examiner has rejected Claims 1, 3-5 15 and 17-19 as allegedly being unpatentably obvious over Hempel et al., in view of Lum et al. ((1993) *J. Cell. Biol.* 1491-1499), to the extent that the claims read on an *in vitro* method for modulating thrombin-induced endothelial cell permeability, by modulating the functional activity of PKCζ. The Examiner's interpretation is discussed above, in connection with the rejection under 35 U.S.C. § 103(a). The Examiner notes that Hempel et al. do not specifically disclose modulation of thrombin-induced vascular permeability. According to the Examiner, Lum et al. teach *in vitro* methods wherein Ca^{2+} mobilization mediated by PKC activation is responsible form thrombin-induced increases in vascular endothelial permeability. The Examiner asserts that in view of the benefits of increasing endothelial cell permeability in a thrombin-induced endothelial mediated activation system as taught by Lum, it would have been *prima facie* obvious for one skilled in the art to modify the method of ischemia-induced endothelial cell permeability disclosed by Hempel et al. to regulate thrombin induced endothelial cell permeability.

Applicants respectfully disagree. To establish a *prima facie* case of obviousness, the Examiner must establish that the skilled artisan would have a reasonable expectation of success

in practicing the claimed invention. *See,* M.P.E.P. §2143.02 "Reasonable Expectation of Success is Required." Further "[a] *prima facie* case of obviousness can be rebutted if the applicant . . . can show 'that the art in any material respect taught away' from the claimed invention." *In re Geisler* 116 F.3d 1465,1469 (Fed. Cir. 1997), quoting *In re Malagrai* 499 F.2d 1297, 1303 (CCPA 1974). As noted above, Hempel et al. do not teach or suggest that modulation agents that affect PKCζ functional activity have any effect on endothelial cell permeability. Importantly, the fact that Hempel et al. tested both PKCα and ζ in assays of endothelial cell permeability and still concluded that PKCα is the relevant isoform of PKC responsible for affects on endothelial cell permeability illustrates the unexpected and surprising nature of Applicants' claimed methods. A skilled artisan, in view of the disclosure of Hempel et al. would be led to believe that modulation agents that alter PKCα activity, rather than any other isoform, would be required to modulate endothelial cell intercellular permeability. Given the teachings of Hempel et al., the skilled artisan would not have any reasonable expectation that modulating PKCζ functional activity, without anything further, would affect endothelial cell permeability.

The disclosure of Lum et al. does not fill the deficiencies of Hempel et al. Specifically, Lum et al. is completely silent regarding protein kinase Cζ, or its potential effects on endothelial cell permeability. Combining the teachings of Lum et al. with the teachings of Hempel et al., would not lead the skilled artisan to reasonably expect that endothelial cell permeability could be modulated by contacting the endothelial cell with a modulation agent that interacts with PKCζ or PKCζ nucleic acids, and affects the functional activity PKCζ. Rather, as discussed above, the combined teachings of Hempel et al. and Lum et al. would lead the skilled artisan to target the α isoform of PKC.

In view of the foregoing, Applicants respectfully submit that the pending claims are not obvious under 35 U.S.C. § 103(a), and request reconsideration and withdrawal of the rejection.

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, Applicant is not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this

application. Applicant reserves the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that Applicant has made any disclaimers or disavowals of any subject matter supported by the present application.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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